AMENDMENTS TO THE CLAIMS

Please amend the application as follows:

In the claims:

1. (Currently Amended): A non-human transgenic animal capable of producing heterologous T-cell receptors, comprising:

human alpha and beta chains;

inactivated endogenous T-cell receptor loci; and

transgenes contained within its genome composed of unrearranged human T-cell receptor loci, wherein expression of the transgenes is controlled by T-cell receptor loci regulatory sequences.

2. (Original): The non-human transgenic animal of claim 1, wherein said inactivated endogenous T-cell receptor loci are α and β chain T-cell receptor loci.

3. (Cancelled).

4. (Currently Amended): The non-human transgenic animal ~~of~~ as in one of claims 1-~~3~~ 2, wherein said human T-cell receptor loci are composed, in operable linkage, of a plurality of human T-cell receptor V genes, and D and /or J and C genes.

5. (Currently Amended): The non-human transgenic animal ~~of~~ as in one of claims 1-~~4~~ 2, wherein said animal is capable of productive VDJC rearrangement and expressing heterologous T-cell receptors.

6. (Currently Amended): The non-human transgenic animal ~~of any~~ as in one of claims 1-~~5~~ 2, wherein said transgenes undergo productive VDJC rearrangement in lymphocytes of said non-human transgenic animal and wherein T-cells express detectable amounts of transgenic TCR in response to antigenic stimulation.

7. (Currently Amended): The non-human transgenic animal ~~of any~~ as in one of claims 1-~~6~~ 2 wherein said non-human transgenic animal produces an immune response to an antigen, said

immune response comprising a population of T-cells reactive to an antigen and wherein the T-cell receptors comprise a human T-cell receptor.

8. (Cancelled).

9. (Withdrawn): The non-human transgenic animal of any one of the preceding claims, further comprising:

transgenes contained within its genome composed of human HLA genes of human MHC loci.

10. (Withdrawn): The non-human transgenic animal of claim 9, wherein said MHC loci contains all human HLA genes.

11. (Withdrawn): The non-human transgenic animal of claim 9, wherein said MHC loci contains a portion of human HLA genes.

12. (Withdrawn): The non-human transgenic animal of any one of claims 9-11, wherein said human HLA genes are MHC class I and MHC class II.

13. (Withdrawn): The non-human transgenic animal of any one of claims 9-12, wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to antigen presented by the human MHC class I receptors and/or reactive to antigen presented by the human MHC class II receptors.

14. (Withdrawn): The non-human transgenic animal of any one of claims 9-13, wherein said human HLA genes are MHC class I.

15. (Withdrawn): The non-human transgenic animal of any one of claims 9-14, wherein said human HLA genes are HLA-A2.

16. (Withdrawn): The non-human transgenic animal of any one of claims 9-15, wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to antigen presented by the human MHC class I receptors.

17. (Withdrawn): The non-human transgenic animal of any one of claims 9-13, wherein said human HLA genes are MHC class II.

18. (Withdrawn): The non-human transgenic animal of any one of claim 17, wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to antigen presented by the human MHC class II receptors.

19. (Withdrawn): The non-human transgenic animal of any one of claims 9-18, wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to the antigen and wherein the T-cell receptors comprise human α and ß chains.

20. (Withdrawn): A non-human transgenic animal of any one of preceding claims, further comprising genes contained within its genome a human co-receptor.

21. (Withdrawn): The non-human transgenic animal of claim 20, wherein said genes encode a CD8 co-receptor and/or a CD4 co-receptor.

22. (Withdrawn): The non-human transgenic animal of claim 20 or claim 21, wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to the antigen and wherein the T-cell receptors comprise human T-cell receptors and co-receptor molecules.

23. (Withdrawn): The non-human transgenic animal of any one of claims 20-22, wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to antigen presented by human MHC class I receptors and/or reactive to antigen presented by human MHC class II receptors.

24. (Withdrawn): The non-human transgenic animal of any one of claims 20-23, wherein said co-receptor is a CD8 co-receptor.

25. (Withdrawn): The non-human transgenic animal any one of claims 20-24, wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to the antigen and wherein the T-cell express on their cell surface human T-cell receptors and co-receptor CD8 molecules.

26. (Withdrawn): The non-human transgenic animal of any one of claims 20-25, wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to antigen presented by human MHC class I receptors.

27. (Withdrawn): The non-human transgenic animal of any one of claims 20-23, wherein said co-receptor is a CD4 co-receptor.

28. (Withdrawn): The non-human transgenic animal of any one of claims 20-23 and 27, wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to the antigen and wherein the T-cells express on their cell surface human T-cell receptors and co-receptor CD4 molecules.

29. (Withdrawn): The non-human transgenic animal of any one of claims 20-23, 27 and 28, wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to antigen presented by human MHC class II receptors.

30. (Currently Amended): The non-human transgenic animal ~~of any~~ as in one of ~~the preceding~~ claims 1-2, wherein said animal is any animal which can be manipulated transgenically.

31. (Currently Amended): The non-human transgenic animal ~~of any~~ as in one of claims 1-~~30~~ 2, wherein said animal is a mouse.

32. (Withdrawn): The non-human transgenic animal of any one of claims 1-30, wherein said animal is a rat.

33. (Withdrawn): The non-human transgenic animal of any one of claims 1-30, wherein said animal is a primate.

34. (Withdrawn): The non-human transgenic animal of any one of claims 1-30, wherein said animal is a chimpanzee.

35. (Withdrawn): The non-human transgenic animal of any one of claims 1-30, wherein said animal is a goat.

36. (Withdrawn): The non-human transgenic animal of any one of claims 1-30, wherein said animal is a pig.

37. (Withdrawn): The non-human transgenic animal of any one of claims 1-30, wherein said animal is a zebrafish.

38. (Original): A method of producing a non-human transgenic animal capable of producing heterologous T-cell receptors comprising the steps of:

inactivating endogenous T-cell receptor loci in an embryo or embryonic stem cell;

inserting transgenes containing active, unrearranged α and β chain human T-cell receptor loci in said embryo or embryonic stem cell, wherein expression of the transgenes is controlled by T-cell receptor loci regulatory sequences;

producing a transgenic animal from said embryo or embryonic stem cell which contains the active human transgene wherein the animal is capable of producing T-cells that express human T-cell receptors; and

breeding the transgenic animal as needed to produce the transgenic animal and its progeny capable of producing heterologous T-cell receptors.

39. (Original): The method of claim 38 wherein said endogenous T-cell receptor loci are α and β chain T-cell receptor loci.

40. (Cancelled):

41. (Original): A method of producing a non-human transgenic animal capable of producing heterologous T-cell receptors comprising the steps of:

inactivating endogenous T-cell receptor loci in an embryo or embryonic stem cell, wherein

said loci are T-cell receptor α or T-cell receptor ß loci;

producing a transgenic animal from said embryo or embryonic stem cell which contains inactivated loci wherein the animal is incapable of expressing said endogenous loci;

crossing a produced transgenic animal having inactivated endogenous T-cell receptor α loci with a produced transgenic animal having inactivated endogenous T-cell receptor ß loci;

selecting progeny having both inactivated endogenous T-cell receptor α and T-cell receptor ß loci;

inserting transgenes containing active, unrearranged human T-cell receptor loci in an embryo or embryonic stem cell wherein said human T-cell receptor loci are human T-cell receptor α or T-cell receptor ß loci, wherein expression of the transgenes is controlled by T-cell receptor loci regulatory sequences;

producing a transgenic animal from said embryo or embryonic stem cell which contains the active human transgene;

crossing a produced transgenic animal having active human T-cell receptor α transgenes with produced transgenic animal having active human T-cell receptor ß-transgenes;

selecting progeny having both active human T-cell receptor α and T-cell receptor ß-transgenes wherein the animal is capable of producing T-cells that express human T-cell receptors;

crossing a produced transgenic animal having both inactivated endogenous T-cell receptor α and T-cell receptor ß loci with a produced transgenic animal having both active human T-cell receptor α and T-cell receptor ß transgenes;

selecting progeny having inactivated endogenous T-cell receptor α and T-cell receptor ß loci and containing active human T-cell receptor α and T-cell receptor ß-transgenes; and
breeding the transgenic animal as needed to produce the transgenic animal and its progeny capable of producing heterologous T-cell receptors.

42. (Currently Amended): The method ~~of any~~ as in one of claims 38-41 wherein said endogenous T-cell receptor loci are inactivated by a functional limitation of the loci.

43. (Currently Amended): The method ~~of any~~ as in one of claims 38-41 wherein said endogenous T-cell receptor loci are inactivated by deleting J segment genes from said loci.

44. (Currently Amended): The method ~~of any~~ as in one of claims 38-41 wherein said endogenous T-cell receptor loci are inactivated by deleting D segment genes from said loci.

45. (Currently Amended): The method ~~of any~~ as in one of claims 38-41 wherein said endogenous T-cell receptor loci are inactivated by deleting C segment genes from said loci.

46. (Currently Amended): The method ~~of any~~ as in one of claims 38-41 wherein said human T-cell receptor loci are unrearranged.

47. (Currently Amended): The method ~~of any~~ as in one of claims 38-~~46~~41 wherein said transgenes containing the active human T-cell receptor loci comprise, in operable linkage, a plurality of human T-cell receptor V genes, and D and/or J and C genes.

48. (Withdrawn): A method of producing a non-human transgenic animal capable of producing heterologous T-cell receptors and heterologous MHC molecules, comprising the steps of:

crossing a transgenic animal expressing heterologous T-cell receptors produced by the method of any one of claims 38-47 with a transgenic animal containing human MHC loci and expressing human MHC molecules;

selecting progeny transgenic animals which express heterologous T-cell receptors and heterologous MHC molecules; and

breeding the transgenic animal as needed to produce the transgenic animal and its progeny capable of producing heterologous T-cell receptors and heterologous MHC molecules.

49. (Withdrawn): The method of claim 48, wherein said MHC loci contains all human HLA genes.

50. (Withdrawn): The method of claim 48 wherein said MHC loci contains a portion of human HLA genes.

51. (Withdrawn): The method of any one of claims 48-50 wherein said human HLA genes are MHC class I and MHC class II.

52. (Withdrawn): The method of any one of claims 48-51 wherein said human HLA genes are MHC class I.

53. (Withdrawn): The method of any one of claims 48-51 wherein said human HLA genes are MHC class II.

54. (Withdrawn): A method of producing a non-human transgenic animal capable of producing heterologous T-cell receptors, heterologous MHC molecules, and heterologous co-receptor molecules, comprising the steps of:

crossing a transgenic animal expressing heterologous T-cell receptors and heterologous MHC molecules produced by the method of any one of claims 48-53 with a transgenic animal containing a heterologous co-receptor genes;

selecting progeny transgenic animals which express heterologous T-cell receptors, heterologous MHC molecules, and heterologous co-receptor molecules; and

breeding the transgenic animal as needed to produce the transgenic animal and its progeny capable of producing heterologous T-cell receptors, heterologous MHC molecules, and heterologous co-receptor molecules.

55. (Withdrawn): The method of claim 54, wherein said heterologous co-receptor is a CD8 co-receptor and a CD4 co-receptor.

56. (Withdrawn): The method of claim 54 wherein said heterologous co-receptor is a CD8 co-receptor.

57. (Withdrawn): The method of any one of claims 54 wherein said heterologous co-receptor is a CD4 co-receptor.

58. (Withdrawn): An immortal cell line capable of producing heterologous T-cell receptors.

59. (Withdrawn): The immortal cell line of claim 58 wherein said T-cell receptors are specific for a particular antigen.

60. (Withdrawn): The immortal cell line of claim 58 or 59 wherein said T-cell receptors are capable of reacting with a chosen peptide/MHC complex of interest.

61. (Withdrawn): An isolated nucleic acid sequence produced by the cell line of any one of claims 58-60 wherein said sequence encodes or is complementary to a sequence that encodes a heterologous T-cell receptor α or β chain.

62. (Withdrawn): An isolated nucleic acid sequence produced by the cell line of any one of claims 58-60 wherein said sequence encodes or is complementary to a sequence that encodes a heterologous T-cell receptor α chain.

63. (Withdrawn): An isolated nucleic acid sequence produced by the cell line of any one of claims 58-60 wherein said sequence encodes or is complementary to a sequence that encodes a heterologous T-cell receptor β chain.

64. (Withdrawn): The isolated nucleic acid of any one of claims 61-63 wherein the nucleic acid is RNA.

65. (Withdrawn): The isolated nucleic acid of any one of claims 61-63 wherein the nucleic acid is DNA.

66. (Withdrawn): Heterologous T-cell receptors produced by the cell line of any one of claims 58-60.

67. (Withdrawn): The heterologous T-cell receptors of claim 66 wherein the receptors are purified or partially purified.

68. (Withdrawn): A method of generating an immortal cell line capable of producing heterologous T-cell receptors, comprising the steps of:

producing a transgenic animal capable of producing heterologous T-cell receptors by the

method of any one of claims 38-57;

inducing an immune response in said animal;

isolating a T-cell expressing human T-cell receptors; and

fusing the isolated T-cell with an immortalizing cell line to generate an immortal cell line capable of producing heterologous T-cell receptors.

69. (Withdrawn): The method of claim 68 wherein said isolated T-cell expresses TCR specific for a particular antigen of interest.

70. (Withdrawn): The method of claim 68 or claim 69 wherein said isolated T-cell expresses TCR capable of reacting with a chosen peptide/MHC complex of interest.

71. (Withdrawn): The method of any one of claims 68-70 wherein said immortalizing cell line is a myeloma cell line.

72. (Withdrawn): An isolated nucleic acid comprising a yeast artificial chromosome operably linked to a human T-cell receptor locus.

73. (Withdrawn): The isolated nucleic acid of claim 72 wherein said human T-cell receptor locus is the α locus.

74. (Withdrawn): The isolated nucleic acid of claim 72 or claim 73 wherein said α locus comprises Vαgenes, Jαgenes and Cαgenes.

75. (Withdrawn): The isolated nucleic acid of any one of claims 72-74 further comprising the regulatory sequences of the α locus.

76. (Withdrawn): The isolated nucleic acid of any one of claims 72-75 further comprising the enhancer region of the α locus.

77. (Withdrawn): The isolated nucleic acid of any one of claims 72-76 further comprising recombination signals of the α locus.

78. (Withdrawn): The isolated nucleic acid of any one of claims 72-77 further comprising the promoter region of the α locus.

79. (Withdrawn): The isolated nucleic acid of any one of claims 72-78 wherein the genes are unrearranged.

80. (Withdrawn): The isolated nucleic acid of any one of claims 72-79 wherein further comprising the regulatory sequences from a heterologous α locus.

81. (Withdrawn): The isolated nucleic acid of any one of claims 72-80 wherein further comprising the enhancer region from a heterologous α locus.

82. (Withdrawn): The isolated nucleic acid of any one of claims 72-81 wherein further comprising the promoter region of a heterologous α locus.

83. (Withdrawn): The isolated nucleic acid of claim 72, wherein said human T-cell receptor locus is the β locus.

84. (Withdrawn): The isolated nucleic acid of claim 72 or claim 83, wherein said β locus comprises Vß genes, Dß genes, Jß genes and Cß genes.

85. (Withdrawn): The isolated nucleic acid of any one of claims 72, 83 or 84 further comprising the regulatory sequences of the ß locus.

86. (Withdrawn): The isolated nucleic acid of any one of claims 72 or 83-85 further comprising the enhancer region of the ß locus.

87. (Withdrawn): The isolated nucleic acid of any one of claims 72 or 83-86 further comprising recombination signals of the ß locus.

88. (Withdrawn): The isolated nucleic acid of any one of claims 72 or 83-87 further comprising the promoter region of the ß locus.

89. (Withdrawn): The isolated nucleic acid of any one of claims 72 or 83-88 wherein the genes are unrearranged.

90. (Withdrawn): The isolated nucleic acid of any one of claims 72, 83-89 wherein further comprising the regulatory sequences from a heterologous TCR ß gene.

91. (Withdrawn): The isolated nucleic acid of any one of claims 72 or 83-90 further comprising the enhancer region of a heterologous ß locus.

92. (Withdrawn): The isolated nucleic acid of any one of claims 72 or 83-91 further comprising the promoter region of a heterologous ß locus.

93. (Withdrawn): An isolated nucleic acid comprising a yeast artificial chromosome operably linked to a human MHC locus.

94. (Withdrawn): The isolated nucleic acid of claim 93 wherein said MHC locus comprises a human HLA class I locus.

95. (Withdrawn): The isolated nucleic acid of claim 93 or claim 94 wherein said MHC locus comprises all human HLA class I genes.

96. (Withdrawn): The isolated nucleic acid of claim 93 or claim 94 wherein said MHC locus comprises a portion of human HLA class I genes.

97. (Withdrawn): The isolated nucleic acid of any one of claims 93-96 wherein said MHC locus is human HLA-A2 gene.

98. (Withdrawn): The isolated nucleic acid of claim 93 wherein said MHC locus comprises a human HLA class II locus.

99. (Withdrawn): The isolated nucleic acid of claim 93 or claim 98 wherein said MHC locus comprises all human HLA class II genes.

100. (Withdrawn): The isolated nucleic acid of any one of claims 93, 98 or 99 wherein said MHC locus comprises a portion of human HLA class II genes.

101. (Withdrawn): An isolated nucleic acid comprising a promoter operably linked to a heterologous co-receptor gene.

102. (Withdrawn): The isolated nucleic acid of claim 101 wherein said heterologous co-receptor gene is a CD4 co-receptor.

103. (Withdrawn): The isolated nucleic acid of claim 101 wherein said heterologous co-receptor gene is a CD8 co-receptor.

104. (Withdrawn): The isolated nucleic acid of claim 101 or claim 103 wherein said CD8 co-receptor is composed of α and ß chains.

105. (Withdrawn): An isolated nucleic acid comprising a targeting vector containing a drug selection marker having targeting sequences homologous to 5' and 3' sequences of an endogenous locus of interest.

106. (Withdrawn): The isolated nucleic acid of claim 105 further comprising a Herpes Simplex Virus thymidine kinase gene cassette.

107. (Withdrawn): The isolated nucleic acid of claim 105 or claim 106 wherein the targeting sequences are capable of directing homologous recombination at the endogenous locus.

108. (Withdrawn): The isolated nucleic acid sequence of any one of claims 105-107 wherein homologous recombination at the endogenous locus results in functional inactivation at the endogenous locus.

109. (Withdrawn): The isolated nucleic acid of any one of claims 105-108 wherein the targeted sequences are endogenous T-cell receptor loci.

110. (Withdrawn): The isolated nucleic acid of any one of claims 105-109 wherein the targeted sequences are endogenous α chain T-cell receptor loci.

111. (Withdrawn): The isolated nucleic acid of any one of claims 105-110 wherein the targeted sequences are endogenous β chain T-cell receptor loci.

~~106~~112. (Currently Amended): A non-human transgenic animal comprising inactivated endogenous T-cell receptor gene loci, said transgenic animal further containing in its genome

transgenes comprising, in operable linkage, a plurality of human T-cell receptor V genes, and their D and /or J and C genes.

~~107~~113. (Currently Amended): A non-human transgenic animal having a germline genome with:

a human T-cell receptor ß chain transgene comprising in operable linkage a plurality of human V genes, and either one or both of the C ß loci and wherein in lymphocytes of said non-human transgenic animal the transgene undergoes productive VDJ rearrangement and produces T-cells expressing TCR human ß chain in detectable amounts in response to antigenic stimulation;

a human T-cell receptor α chain transgene with plurality of human V gene segments, human J gene segments, the human C α coding exon, and a human 3' downstream α-enhancer; and wherein in lymphocytes of said non-human transgenic animal the transgene undergoes productive VDJ rearrangement and produces T-cells expressing TCR human α-chain in detectable amounts in response to antigenic stimulation;

an endogenous TCR ß chain loci having an inactivated ß chain gene; and

an endogenous TCR α chain loci having an inactivated α chain gene.